REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as proposed to be amended, are respectfully requested in light of the remarks which follow.

The courtesy of the interview granted by Examiner Kishore to the undersigned on May 29, 2002, is gratefully acknowledged.

Upon entry of the foregoing amendment, Claims 25, 26, 28-51, 53-81, 83-111 and 113-114 will be in the application. Claims 2-24 were cancelled upon filing on December 14, 2000; Claims 52, 82 and 112 were cancelled November 5, 2001; and Claim 27 has been proposed to be cancelled above.

Claim 27 has been proposed to be cancelled as redundant in light of the proposed amendment of Claim 25.

Claim 25, drawn to a cosmetic or dermatological method for treating sensitive skin, has been proposed to be amended above to recite that the sensitive skin is characterized by exhibiting at least one symptom selected from the group consisting of tingling, prickling, itching, pruritus, overheating, discomfort, tugging sensations, desquamation and erythema, in reaction to at least one external factor which is not an allergen. These symptoms are those noted on page 2 of the specification, see especially lines 3-5 and 20-26 and page 3, lines 1-5. As further noted on page 2, lines 7-16, sensitive skin is not the same as allergic skin. Allergic skin reacts to an external agent which is an allergen, which triggers an allergic reaction; this is an immunological process. On the other hand, sensitive skin responds to external factors which are not allergens; this is not an immunological process.

Thus, there is a clear basis in the specification for the language added to Claim 25 and no new matter has been introduced. Further, by specifying in Claim 25 the characteristic responses of sensitive skin to external factors which are not allergens, Applicants have made it perfectly clear that they are claiming a method for treating skin which is characterized by exhibiting one or more particular symptoms in response to one or more non-allergy-causing external factors. The proposed language is believed to appropriately address concerns, expressed by the Examiner at the interview, that some of the enumerated symptoms may also be exhibited when allergic skin reacts to an allergen. It is also believed that allowance of Claim 25 as proposed to be amended would be consistent with the prosecution of the parent application, now U.S. Patent No. 6,235,291 (copy appended). A terminal disclaimer vis-à-vis the '291 patent has already been submitted herein, and all of the art relied upon here was overcome therein.

Claims 55 and 85 have been proposed to be amended above simply to make typographical and linguistic corrections which do not change the scope of these claims. Claim 55 has always been drawn to a method for treating sensitive, but not allergic, skin, while Claim 85 has always been drawn to a method for treating capsaicin-sensitive skin. It was already established during prosecution of the parent application that the phraseology "sensitive, but not allergic, skin" distinguished from the same art as is relied upon here. It was further established in the parent, and is disclosed on pages 3-4 of the specification, that there is a correlation between sensitive skin and skin which reacts to capsaicin. Thus, it is believed that allowance of Claims 55 and 85 would also be consistent with the prosecution of the parent application. Indeed, Claims 55 and 85 and their dependent claims were first

submitted in the parent application because they were believed to be consistent with what the Examiner had agreed to allow therein; however, these claims were not entered therein because they were first presented after final rejection. Further, Examiner Kishore indicated at the recent interview in the present application that the language of Claims 55 and 85 was consistent with his reasons for allowance in the parent.

To further support Applicants' position, there is filed herewith a copy of a study report relating to sensitive skin, allergic skin and cutaneous reactivity to capsaicin. This study reinforces Applicants' position that cutaneous reactivity to capsaicin does not enable one to distinguish persons with allergic skin from those without allergic skin, whereas cutaneous reactivity to capsaicin does enable one to distinguish persons with sensitive skin from those without sensitive skin. If both sensitive and allergic skin groups were identical, such differentiation would not occur. The study shows also that there is no significant correlation between the allergic skin population and the population having sensitive skin and that, indeed allergic skin and sensitive skin represent two different groups of population.

It is believed that it is quite apparent from the foregoing that the claims as proposed to be amended hereinabove are allowable for the reasons advanced above and throughout the prosecution of the parent application. Nevertheless, Applicants will address below the various rejections set forth in the January 14, 2002 Official Action. First, however, we wish to summarize the interview conducted in the parent application and referred to at the May 29, 2002 interview herein, and to summarize the present invention.

At the interview in the parent case, Examiner Kishore, several representatives of the Assignee, L'ORÉAL, the inventor Olivier de Lacharriere, and Norman Stepno were present. During that interview, the inventor presented substantial information in the form of a slide presentation, and a lengthy discussion explaining the significant differences between sensitive and allergic skin, as well as the capsaicin test developed by the Assignee to determine whether a subject has sensitive skin. It was further explained at length during the interview why the prior art fails to teach or suggest the claimed invention. In particular, it was noted that there is no statistical correlation between subjects having sensitive and allergic skin, as these are truly different disorders. Based thereon, it was argued that methods for treating allergic skin, and especially relating to treatment by injection, have no relevance to the claimed invention.

It is further noted that the Examiner agreed with Applicants' position at the interview in the parent, and advised that he would allow that application, contingent on the submission of Terminal Disclaimers to overcome double patenting issues (which were thereafter filed in the parent and have also been submitted herein). Also, the Applicants' representative noted that the Examiner had agreed that the novel and unobvious feature of the invention comprises a method of treating sensitive but not allergic or capsaicin-sensitive skin by topical administration of at least a substance P antagonist and optionally an irritant which would otherwise cause irritation to sensitive skin.

Essentially, by the present amendments, the claims are believed to be consistent with the discussion at the interview. In particular, the claims refer to treatment of sensitive, but not allergic, skin (Claim 55 and its dependent claims) or to treatment of

capsaicin-sensitive skin (Claim 85 and its dependent claims) or to treatment of sensitive skin which exhibits at least one of a group of specified conditions in response to at least one external factor which is not an allergen (Claim 25 and its dependent claims). As discussed during the interview in the parent, and substantiated by the data and information presented by the inventor as well as by the report submitted herewith, sensitive skin and allergic skin are distinct conditions.

The prior art rejections are discussed below merely for file wrapper completeness as it is believed that these rejections are moot in view of the foregoing remarks.

Claims 25-28, 32-34, 45-46, 51-52, 55-58, 62-64, 75-76, 85-88, 97, 101, 105-106, 111, 112 and 114 have been rejected under 35 U.S.C. §102(b) as anticipated by, and under 35 U.S.C. §103 as unpatentable over, WO 93/14084. In addition, all of the claims have been rejected under 35 U.S.C. §103 as assertedly being unpatentable over the combination of Wallengren (*Contact Dermatitis*, 1988), Wallengren (*Br. J. Dermatitis*, 1991), in combination with WO 83/01252 and/or WO 93/14084. These rejections are respectfully traversed. As discussed, it is believed that the Examiner has already acknowledged that the prior art does not teach or suggest treatment or prevention of sensitive skin as set forth in Claims 25, 55 and 85 (the independent claims) as proposed to be amended.

Prior to specifically addressing the §§ 102 and 103 rejections, the claimed invention is discussed below. It is believed that this will facilitate an understanding as to why the claimed invention is in no way suggested by the prior art. Indeed, at least one of the references cited by the Examiner teaches against the efficacy of the claimed methods.

Essentially, the present invention hinges on several discoveries. The first discovery is that sensitive skin and the various symptoms associated therewith, which are triggered by various different external factors, e.g., changes in temperature, wind, friction, as well as others, is distinct from allergic skin, and can be detected based on the reactivity or lack of reactivity of such skin to topical application of capsaicin. Specifically, it has been discovered that persons with sensitive skin develop an erythema shortly after topical capsaicin application, whereas those with non-sensitive skin do not. Related thereto, it has been discovered that sensitive skin reactions are associated with the release of specific neuropeptides, in particular tachykinins, and most especially substance P. While it had been known prior to the present invention that substance P had some involvement in pain transmission and in various diseases including central nervous system diseases, as well as respiratory, inflammatory, gastrointestinal and rheumatic diseases, and other skin disorders, in particular eczema, it had not been known that the release of substance P was significant with respect to the etiology and the various symptoms associated with sensitive skin.

Secondly, it further was unknown prior to the present invention that the symptoms of sensitive skin could be prevented or alleviated after onset by the topical administration of a substance P antagonist. This is a surprising discovery, and would have been unexpected even if it had been known that substance P was involved in sensitive skin reactions. This result is surprising for several reasons. For example, as there exist different tachykinins and other neuromediators, it could not have been reasonably predicted that intervention in the production or release of one neuromediator would not have been sufficient to treat or

prevent sensitive skin. Often times, biological and neurological phenomena involve the interaction of several different substances. Based thereon, it was surprising that merely antagonizing substance P is sufficient to inhibit sensitive skin as it was quite possible that other neuromediators or substances would have been involved in eliciting sensitive skin reactions.

Moreover, it was also surprising that the topical administration of a substance P antagonist would effectively prevent or treat sensitive skin. In this regard, it is well-known that the particular mode of administration can be highly significant in the context of treatment. In the present case, it was heretofore unknown that a topically administered substance P antagonist would be able to reach the requisite target (receptors involved in substance P release and production) and thereby inhibit substance P release or production to an extent sufficient to be prophylactically or therapeutically effective. For example, the substance P antagonist might not have been able to reach the desired target, or not to such an extent to be useful.

Also, aside from the fact that the efficacy of topical administration was surprising based on the state of the art and lack of understanding as to the etiology of sensitive skin, it is also imperative to the practical usage of the invention. With respect thereto, while sensitive skin is quite troublesome to persons who have such condition, it is a condition wherein effective treatment necessarily must be cost-effective and convenient. Essentially, persons who suffer from sensitive skin will likely be unwilling to prevent or treat such condition by means of an injection, or other invasive route of drug administration. Rather, it is a condition that is most appropriately treated in the context of a cosmetic regimen,

wherein such condition is typically manifested. (It is often manifested upon topical application of active ingredients utilized in cosmetic or dermatologic regimens.) Therefore, the present inventors have solved a significant problem, i.e., they have developed a practical and convenient means of treating and preventing sensitive skin which can be readily utilized in the context of dermatological and cosmetic regimens. By contrast, had topical administration been ineffective, as was entirely possible, the present invention would not have had the same practical significance. For example, the present invention provides for topical administration of irritants to persons having sensitive skin, or in greater amounts, than would otherwise have been feasible. This is significant, especially given the irritating effects of many desirable topically administered agents to users having sensitive skin. Therefore, with this understanding of the invention, the prior art is now addressed below.

Several references have been cited as allegedly disclosing or suggesting the use of a substance P antagonist to treat or prevent sensitive skin. This is notwithstanding the fact that neither Wallengren (*Contact Dermatitis*, 1988) nor Wallengren et al (*Br. J. Dermatitis*, 1991) relates to treatment or prevention of sensitive skin reactions; rather, both of the Wallengren references instead relate to treatment or prevention of allergic skin reactions, specifically allergic contact dermatitis. Likewise, WO 83/01252 and WO 83/14084 do not disclose or suggest treating sensitive skin; rather, they relate to certain conditions which are allergic conditions or which are manifestations of allergic reactions. There is positively no disclosure in the references of the possibility of treating sensitive skin, which reacts to non-allergy-causing factors, not to allergens.

As discussed in the instant specification, and substantiated in the parent application by a prior 37 C.F.R. §1.132 Declaration by Lionel Breton, Ph.D., an inventor of this application, and the data presented by the other inventor, Dr. de Lacharriere, at the interview, sensitive skin and allergic skin are dissimilar in etiology, symptoms and treatment. Also, the Wallengren references are further not germane to the claimed methods as neither of these references teaches or suggests topical administration of a substance P antagonist to treat skin irritation. Rather, in both Wallengren references, the exemplified substance P antagonist (Spantide) is administered via injection.

Specifically, the earlier (1988) Wallengren reference (*Contact Dermatitis*) describes experiments which suggest that the injection of a substance P antagonist may alleviate allergic contact dermatitis in subjects which are injected with a mediator of such allergic contact dermatitis, i.e., nickel sulfate.

Specifically, Wallengren (1988) teaches administration of a substance P antagonist (Spantide) via injection. There is no indication that Spantide would be effective if topically administered. In fact, Applicants respectfully maintain that the reference teaches against topically administrable forms given the fact that in their experiments they administer both the irritating substance (nickel sulfate) (elicitor of allergic skin reaction) and the substance P antagonist (Spantide) via injection. Also, as discussed above, the reference relates to treatment of allergic skin reactions, not sensitive skin as claimed herein.

It is quite clear from Wallengren (1988) that the studied irritant, nickel sulfate, is exemplary of substances that cause irritation via allergic responses, i.e., an immunological (allergic contact dermatitis) response. This is clear, e.g., based on the disclosure at page

352, right-hand column, wherein Wallengren refers to "the immunological process in which Spantide interferes". This is further consistent with their prophetic disclosure suggesting the concomitant administration of a specific antigen and a substance P antagonist. Thus, in Wallengren (1988), the irritant is an antigen which elicits an immunological response, i.e., an allergic contact dermatitis response, and the condition treated by Wallengren is immunological in nature, i.e., allergic skin. Sensitive skin is not an immunologic or allergic disorder.

The Examiner previously equated treatment of allergic skin, i.e., allergic contact dermatitis, to treatment of sensitive skin. However, as explained at the interview in the parent, this is improper. Indeed, as previously argued, sensitive skin is not the same as allergic skin. Allergic skin and allergic skin reactions involve specific immunological responses that are triggered by specific immunogens, i.e., antigens that induce an allergic response in specific persons that are allergic to such antigens.

By contrast, as explained in some detail in the instant application, and supported by the previous 37 C.F.R. §1.132 Declaration of Lionel Breton, Ph.D. in the parent, and by the data presented by Dr. de Lacharrière during the interview, sensitive skin is a non-allergic condition that is aspecific in cause, i.e., which can be triggered by a variety of factors, including rubbing, soap, surfactants, emotions, changes in the environment (cold, heat). While allergic reactions are only manifested when an allergen is present, sensitive skin responses can occur in the absence of such a substance, e.g., they can be triggered by mere contact or temperature changes. *See* paragraph 6 of Breton Declaration, a copy of

which is appended. Moreover, methods of treating sensitive skin and allergic skin cannot be equated.

Specifically, while sensitive skin and allergic skin show some common clinical signs, such as pruritus, given their different etiologies, they must generally be treated differently. Hence, there would be no reasonable expectation based on Wallengren (1988) that a substance (Spantide) which inhibited an allergic response elicited by an antigen would similarly inhibit a non-allergic sensitive skin reaction induced by an active agent utilized in a topical cosmetic regimen. The same can be said of the WO citations.

In fact, Dr. Breton, an expert in the art, specifically states in his earlier Declaration that "it could not have been reasonably predicted at the time of the invention that compounds suitable for the treatment of allergic skin would have any beneficial effect in the treatment of sensitive skin." In support thereof, Dr. Breton refers to the inefficacy of immunosuppressive drugs which effectively treat allergic skin but which have no benefit in treatment of sensitive skin.

In further support of the non-equivalency of allergic *vis-à-vis* sensitive skin, and substances which elicit allergic versus sensitive skin responses, Applicants provided at the interview a slide presentation by Dr. de Lacharrière, also an inventor of this application, which contained additional experimental data supporting the significant differences between sensitive and allergic skin reactions, and methods for the treatment thereof.

For example, it was noted at the interview in the parent that these experimental data indicated that there is little overlap between persons that develop sensitive skin reactions and persons who develop allergic skin reactions upon topical application of an irritant

(perfume). Specifically, only 4.5% of persons having a sensitive skin reaction to the tested irritant (perfume) also exhibited an allergic reaction. Note also the report filed herewith.

Also, the inventor showed data at the interview in the parent relating to a number of allergens substantiating that allergic skin reactions and sensitive skin reactions have little or no statistical overlap as these conditions are distinct in nature. Again, see the report filed herewith.

Thus, based on the foregoing, it was persuasively argued at the interview, and maintained herein, that Wallengren (1988) fails to teach or suggest the claimed topical treatment of sensitive skin as the reference is limited in its disclosure to treatment of a different skin disorder by a different mode of administration (injection).

Turning now to the later Wallengren reference (*Br. J. Dermatology*, 1991), this reference is similar in its teachings to the earlier Wallengren reference (1988). Essentially, Wallengren (1991) contains the results of a later study by Wallengren wherein she again studied the effects of the injection of Spantide on the immunological, i.e., allergic, responses induced by different antigens. Specifically, the author states in her discussion that the results of this study indicate that "only the immunological reactions (immunological contact urticaria and tuberculin reaction) were suppressed by the SP antagonist Spantide."

Also, Wallengren (1991) goes on to say that non-immunological contact urticaria (NICU) which does not involve immunological processes was not effectively treated by the disclosed treatment (injection of Spantide). Still further, Wallengren states at page 327, right-hand column, that "only the immunological contact urticaria was suppressed by

pretreatment with Spantide, suggesting that SP is involved in the pathogenesis of the immediate allergic reaction."

Thus, based on the author's own conclusions, the reasonable expectation would have been that the administration of a substance P antagonist would have no benefit in the treatment of sensitive skin because of its non-immunological etiology. Also, this reference should be accorded greater weight than the first Wallengren reference because the authors' conclusions take into account the results of a later study which suggests that administration of a substance P antagonist had no effect on non-immunologically induced skin irritation.

Also, as with the earlier Wallengren reference, Wallengren (1991) is similarly deficient in that it fails to teach topical administration of a substance P antagonist as claimed herein. Rather, in Wallengren (1991), the substance P antagonist is again administered via injection and is administered separately from the tested substances which elicited immunological or non-immunological based irritation. Thus, the latter Wallengren reference clearly teaches against the efficacy of the claimed topical regimen for treatment of sensitive skin, a non-immunological skin disorder.

WO 83/01252 and WO 93/14084 also do not teach or suggest the claimed methods. These references are again cited based on their general disclosure relating to topically administrable substance P antagonist-containing compositions. However, Applicants respectfully traverse the rejection as these references likewise do not provide the requisite motivation to topically administer at least one substance P antagonist as a means of treating or preventing sensitive skin as claimed in the claims as proposed to be amended herein.

Still further, the '084 reference is deficient in that the substance P antagonists disclosed therein are of the NK_2 type. That is to say, they antagonize binding or interaction of substance P with NK_2 receptors. However, NK_2 receptors are not found in the skin. Rather, only NK_1 receptors are found in human skin. In support thereof, Applicants provided in the parent an Abstract, Bianchi *et al*, *J. Eur Acad Dermatol Venereol.*, 1999 Jan 12(1):6-10. This Abstract, also previously made of record in the parent, makes clear that the substance P receptors found in human skin are of the NK_1 type. Hence, this substantiates that the rejections based thereon are clearly improper as the topical compositions described by the '084 reference would not function effectively to treat or prevent sensitive skin irritation as claimed, given the fact that the NK_2 receptors are not found in human skin.

Moreover, the conclusions of the Examiner are respectfully submitted to be untenable. The irritation alleviated by the teachings of the references (Wallengren) is immunological or allergic in nature, i.e., it involves suppression of an antibody-antigen response. Contrary to the Office Action, there is no information in either Wallengren reference, or in the WO references, which would suggest a correlation between topical application of a substance P antagonist and alleviation of non-immunological, sensitive skin reactions.

In fact, Wallengren (1991) concludes, based on her studies, that only immunological contact urticaria was suppressed by pretreatment with Spantide, "suggesting that SP is [only] involved in the pathogenesis of the immediate allergic reaction."

Therefore, even assuming that it could have been reasonably predicted that substance P antagonists were effective upon topical administration, in view of Wallengren's own conclusions based on their results, this would not be sufficient to suggest that topical administration of such an antagonist would alleviate irritation associated with sensitive skin (because of its non-immunological etiology.) With respect thereto, it is again noted that the Examiner has conceded that sensitive skin is distinct from allergic skin based on the earlier submitted 37 C.F.R. §1.132 Declaration in the parent, and the data and comments submitted at the previous interview in the parent.

Also, it was not reasonably predictable that a topically administered substance P antagonist would inhibit substance P induced by a mediator of sensitive skin reactions (e.g., irritant). While some of the references suggest topically administrable substance P antagonist-containing compositions, there is no reference of record which would reasonably suggest that a topically administered substance P antagonist would effectively treat or prevent sensitive skin reactions. Also, as argued *supra*, the modulation of immediate and delayed (allergic) reactions would not suggest the efficacy of the subject topically administrable cosmetic composition, particularly given the fact that Wallengren (1991) expressly indicates that their treatment (administration of Spantide via injection) had no effect on non-immunological induced skin urticaria. Indeed, as discussed *supra*, the prior art was completely unaware of the correlation between sensitive skin and the release of substance P and its effective treatment using a substance that antagonizes substance P. Thus, it was <u>not</u> reasonable to expect that sensitive skin irritation elicited by topical administration of an active agent used in a topical cosmetic regimen would be alleviated by

a topically administered substance P antagonist. To the contrary, both the problem (that sensitive skin reactions are elicited by the release of substance P) and the solution (that such reactions could be effectively alleviated by topical administration of a substance P antagonist) were heretofore unknown. Therefore, withdrawal of the record §§ 102 and 103 rejections is respectfully believed to be in order.

Based on the foregoing, this application is believed to be in condition for allowance. A Notice to that effect is respectfully solicited. However, if any issues remain outstanding after consideration of this Reply, the Examiner is respectfully requested to contact the undersigned so that prosecution may be expedited.

Respectfully submitted,

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Attachment to Reply and Amendment Following Final Rejection dated July 11, 2002

Marked-up Claims 25, 55 and 85

25. (Twice Amended) A cosmetic or dermatological method for treating sensitive skin of an individual in need of such treatment, [such] said sensitive skin having or developing neurogenic manifestations of dyesthesia caused by the release of substance P therein, [the] said sensitive skin being characterized by exhibiting at least one symptom selected from the group consisting of tingling, prickling, itching, pruritus, overheating, discomfort, tugging sensations, desquamation and erythema, in reaction to at least one external factor which is not an allergen; said method comprising topically applying to said sensitive skin an effective amount of at least one substance P antagonist-containing composition, and wherein said effective amount of said at least one substance P antagonist is formulated into a topically applicable cosmetically- or dermatologically-acceptable medium therefor.

55. (Twice Amended) A cosmetic [of] or dermatological method for treating sensitive, but not allergic, skin of an individual in need of such treatment, [such] said sensitive skin having or developing neurogenic manifestations of dyesthesia caused by the release of substance P therein, [the] said method comprising topically applying to said sensitive skin an effective amount of at least one substance P antagonist-containing composition, and wherein said effective amount of said at least one substance P antagonist

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Marked-up Claims 25, 55 and 85

is formulated into a topically applicable cosmetically- or dermatologically-acceptable medium therefor.

85. (Twice Amended) A cosmetic or [dermatoligical] dermatological method for treating capsaicin-sensitive skin of an individual in need of such treatment, [such] said sensitive skin having or developing neurogenic manifestations of dyesthesia caused by the release of substance P therein, [the] said method comprising topically applying to said capsaicin-sensitive skin an effective amount of at least one substance P antagonist-containing composition, and wherein said at least one substance P antagonist is formulated into a topically applicable cosmetically- or dermatologically-acceptable medium therefor.